1/29/04

L Number	Hits	Search Text	DB	Time stamp
1	343	(parenteral) and (bisphosphonate)	USPAT; US-PGPUB	2004/01/29 15:36
2	358	(parenteral) and (bisphosphonate)	USPAT; US-PGPUB; DERWENT	2004/01/29 15:36
3	17	((parenteral) and (bisphosphonate)) and zolendronate	USPAT; US-PGPUB; DERWENT	2004/01/29 16:52
4	381	restenosis and intra-arterial	USPAT; US-PGPUB; DERWENT	2004/01/29 16:52
5	34	restenosis and (intra-arterial adj injection)	USPAT; US-PGPUB; DERWENT	2004/01/29 16:52
6	3887	restenosis and (intra-arterial adj injection or infusion)	USPAT; US-PGPUB; DERWENT	2004/01/29 16:53
7	54	restenosis and (intra-arterial adj (injection or infusion))	USPAT; US-PGPUB; DERWENT	2004/01/29 16:53
-	1	"6416964" .pn.	USPAT; US-PGPUB	2004/01/29 15:02
-	3786	intra-arterial	USPAT; US-PGPUB	2004/01/29 12:01
-	12	intra-arterial and bisphosphonate	USPAT; US-PGPUB	2004/01/29 11:45
-	3992	intra-arterial	USPAT; US-PGPUB; DERWENT	2004/01/29 11:45
-	12	intra-arterial and bisphosphonate	USPAT; US-PGPUB; DERWENT	2004/01/29 11:45
-	9734	intra-arterial or intraarterial	USPAT; US-PGPUB	2004/01/29 12:06
-	2145	(intra-arterial or intraarterial) and (angiogenesis or angiogenetic)	USPAT; US-PGPUB	2004/01/29 12:07
-	1885	((intra-arterial or intraarterial) and (angiogenesis or angiogenetic)) and (myocardial or arthritis or osteoarthritis or tumour)	USPAT; US-PGPUB	2004/01/29 12:02
-	1883	(((intra-arterial or intraarterial) and (angiogenesis or angiogenetic)) and (myocardial or arthritis or osteoarthritis or tumour)) and (treating or treatment or therapy)	USPAT; US-PGPUB	2004/01/29 12:03
-	1	((((intra-arterial or intraarterial) and (angiogenesis or angiogenetic)) and (myocardial or arthritis or osteoarthritis or tumour)) and (treating or treatment or therapy)) and bisphosphonate	USPAT; US-PGPUB	2004/01/29 12:03
-	128	((((intra-arterial or intraarterial) and (angiogenesis or angiogenetic)) and (myocardial or arthritis or osteoarthritis or tumour)) and (treating or treatment or therapy)) and embolism	USPAT; US-PGPUB	2004/01/29 12:03
-	1215	(intra-arterial or intraarterial or intra-arterially or intraarterially) adj (injection or administration or adminitering)	USPAT; US-PGPUB	2004/01/29 13:05
-	163	((intra-arterial or intraarterial or intra-arterially or intraarterially) adj (injection or administration or adminitering)) and (angiogenesis or angiogenetic)	USPAT; US-PGPUB	2004/01/29 12:07
-	10094	intraartery or intraarterial or intra-arterial	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/01/29 13:03

-	32	(intraartery or intraarterial or intra-arterial) and bisphosphonate	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/01/29 13:03
-	77310	((intra-arterial or intraarterial or intra-arterially or intraarterially) adj (injection or administration or adminitering)) or parenteral	USPAT; US-PGPUB	2004/01/29 13:05
-	345	(((intra-arterial or intraarterial or intra-arterially or intraarterially) adj (injection or administration or adminitering)) or parenteral) and bisphosphonate	USPAT; US-PGPUB	2004/01/29 13:07
-	55	((((intra-arterial or intraarterial or intra-arterially or intraarterially) adj (injection or administration or adminitering)) or parenteral) and bisphosphonate) and hepatic	USPAT; US-PGPUB	2004/01/29 15:36

(FILE 'HOME' ENTERED AT 11:46:58 ON 29 JAN 2004)

FILE 'MEDLINE, BIOSIS, EMBASE' ENTERED AT 11:47:09 ON 29 JAN 2004

L1	11036	S BISPHOSPHONATE OR PAMIDRONIC OR ZOLEDRONIC
L2	31599	S INTRA-ARTERIAL
L3	59312	S INTRA-ARTERIAL OR INTRAARTERIAL
L4	13	S L1 AND L3
L5	9	DUP REM L4 (4 DUPLICATES REMOVED)
L6	1297352	S L3 OR ARTERY OR ARTERIAL
L7	108	S L6 AND L1
L8	65	DUP REM L7 (43 DUPLICATES REMOVED)
L9	65	FOCUS L8 1-
L10	64	S L9 NOT INTRA-ARTERIAL
L11	58	S L9 NOT INTRAARTERIAL

L14 ANSWER 4 OF 9 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

ACCESSION NUMBER: 2000429151 EMBASE

TITLE: Antitumor effect of alendoronate on malignant hepatic tumor.

AUTHOR: Oida T.; Amano S.; Mori K.-I.; Niki M.; Inoue M.; Horii A.; Takeuchi S.; Haga N.; Miyake H.; Fukuzawa M.

CORPORATE SOURCE: Dr. T. Oida, Department of Surgery, Yokohama Central Hospital, Yamashita-Cho, Naka-ku, Yokohama 231-8553, Japan

SOURCE: Biotherapy, (2000) 14/10 (1017-1022).
Refs: 12
ISSN: 0914-2223 CODEN: BITPE

COUNTRY: Japan

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
048 Gastroenterology

LANGUAGE: Japanese

SUMMARY LANGUAGE: English; Japanese

AB Parathyroid hormone-Related protein (PTHrP) and other osteoclast stimulation factors, which are produced by malignant tumor cells, stimulate the osteoclast. As a result, hypercalcemia seems to be induced, and the bone resorption increases. Many reports have proven that **bisphosphonate**, which inhibits bone resorption, is effective for this hypercalcemia. We **administered** alendronate (Onclast.RTM.), which is a kind of **bisphosphonate**, to hypercalcemia patients with malignant liver tumors. As a result, it was observed that the serum calcium value decreased, and that some tumor marker values improved simultaneously. Thus, it was supposed that alendoronate has an antitumor effect in addition to the action of suppressing the osteoclast, and we studied the mechanism of the antitumor effect. Onclast.RTM. was **administered** directly from the hepatic **artery** in order to investgate the effect on hepatic tumor of Onclast.RTM.. Intra-Tumoral blood flow decreased somewhat after the **administration** of Onclast.RTM. in the ultrasonic testing. No difference was observed on imaged angiograms when hepatic **artery** imaging examinations were compared around the time of **administration** of Onclast.RTM.. Although no obvious change in the histological findings was recognized on the light microscopic level in stroma of the tumor, electron microscope examination revealed an increase in vacuolization and formation of apoptotic vesicles in the vascular endothelial cells. In addition, these endothelial cells were found to have morphologically hyperplastic shapes by electron microscopy. In the non-Tumor tissue collected from the circumference of the tumor, such change was not observed. From these results, it is suggested that the **administration** of Onclast.RTM. caused some form of injury in tumor endothelial cells. In conclusion, it is indicated that **bisphosphonate** is a possibile tumor vessel embolism material which selectively affects the endothelial cells of tumors.

CCESSION NUMBER: 2000471489 MEDLINE
DOCUMENT NUMBER: 20420657 PubMed ID: 10963835
TITLE: Administration routes and delivery systems of **bisphosphonates** for the treatment of bone resorption.
AUTHOR: Ezra A; Golomb G
CORPORATE SOURCE: Department of Pharmaceutics, School of Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem, POB 12065, 91120, Jerusalem, Israel.
SOURCE: Adv Drug Deliv Rev, (2000 Aug 31) 42 (3) 175-95. Ref: 119
Journal code: 8710523. ISSN: 0169-409X.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20001012
Last Updated on STN: 20001012
Entered Medline: 20001005

AB Geminal **bisphosphonates** (BPs) are a class of drugs considered to be stable analogs of pyrophosphate (P-O-P), a physiological regulator of calcification and bone resorption. A number of BPs have been approved for clinical use in Paget's disease, hypercalcemia of malignancy, and osteoporosis. The major disadvantage of the clinically utilized BPs is their poor oral absorption from the GI tract, typically less than 1% is absorbed. In addition, the BPs have been associated with adverse gastrointestinal effects in humans. The challenge for novel drug delivery systems is to achieve improved bioavailability and safety. In the first part of this review, we discuss the bioavailability of BPs, the effect of food on the absorption of BPs, the mechanism of BPs' absorption and the adverse gastrointestinal effects. In the second part of the review, various methods that have been used for improving the bioavailability of BPs are described. Dosage form strategies reviewed include the use of particular formulations for increasing oral absorption as well as decreasing adverse gastrointestinal effects, absorption enhancers, BP compounds and the solubility of their calcium complex/salts, and the prodrug approach. Because of the poor GI absorption, attempts have been made to enhance the bioavailability of BPs by several **parenteral** routes other than i.v. injections. Description of nasal administration, s.c. and i.m. injections, BP implants and targeted osteotropic delivery systems are reviewed.

17 ANSWER 48 OF 139 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:640549 CAPLUS
DOCUMENT NUMBER: 127:288184
TITLE: Treatment of osteoporosis and metabolic bone disorders with nitric oxide substrate and/or donors
INVENTOR(S): Yallampalli, Chandrasekhar; Wilamawansa, Sunil J.
PATENT ASSIGNEE(S): Board of Regents, the University of Texas System, USA; Yallampalli, Chandrasekhar; Wilamawansa, Sunil J.
SOURCE: PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9734609	A1	19970925	WO 1997-US4311	19970318
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5898038	A	19990427	US 1996-616470	19960319
AU 9726579	A1	19971010	AU 1997-26579	19970318
EP 954319	A1	19991110	EP 1997-918484	19970318
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 6133320	A	20001017	US 1998-177978	19981022

PRIORITY APPLN. INFO.: US 1996-616470 A2 19960319
WO 1997-US4311 W 19970318

AB Primary and secondary osteoporosis in a female or a male mammal in any age treated by administering thereto a nitric oxide synthase substrate, a nitric oxide donor or both, optionally; in further combination with one or more of an estrogen, a progestin, a **bisphosphonate**, an anabolic steroid, testosterone, a flavinoid, vitamin D analog or a calcitonin. Nitric oxide substrate or donor also can be combined with one or more of the other medication acting on bone, such as **bisphosphonate**, calcitonin, fluoride, androgen, vitamin D analog, and other novel therapeutic agents. Either nitric oxide donor or substrate by itself or in combination with other medications as described above can be used in both males and females, for prevention and treatment of osteopenia or osteoporosis, and other metabolic bone disorders.

L17 ANSWER 43 OF 139 MEDLINE on STN
ACCESSION NUMBER: 89283583 MEDLINE
DOCUMENT NUMBER: 89283583 PubMed ID: 2525271
TITLE: [Treatment of Paget's disease].
Traitement de la maladie de Paget.
AUTHOR: Audran M; Basle M F
SOURCE: REVUE DU PRATICIEN, (1989 Apr 27) 39 (13) 1137-42.
Journal code: 0404334. ISSN: 0035-2640.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: French
FILE SEGMENT: Foreign
ENTRY MONTH: 198907
ENTRY DATE: Entered STN: 19900309
Last Updated on STN: 19900309
Entered Medline: 19890725

AB The advent of compounds that oppose excessive bone resorption is a remarkable advance in the treatment of Paget's disease, the course of which can be controlled, in almost every case, by calcitonin and **bisphosphonates**. This treatment aims at limiting the hypertrophy and deformation of bones, thereby reducing the incidence of neurosensory and orthopaedic complications, principal causes of disablement. It follows that those forms of the disease that are characterized by strong biochemical activity and/or bone lesions resulting in neurosensory suffering of articular impairment of the lower limbs must be treated actively. In every case, vitamin D or calcium deficiencies likely to induce hyperparathyroidism must be corrected. Orthopaedic appliances on long bones or lower limb articulations are sometimes necessary. New drugs (e.g. **bisphosphonates** with greater activity) and different pharmaceutical preparations or modes of administration (e.g. short **parenteral** courses of **bisphosphonates**, calcitonin in nasal spray) might soon increase the possibilities of treatment and provide an even better control of Paget's disease of bone.

CCESSION NUMBER: 97287837 MEDLINE
DOCUMENT NUMBER: 97287837 PubMed ID: 9142965
TITLE: Analgesic effect of **bisphosphonates** on bone pain in breast cancer patients: a review article.
AUTHOR: Strang P
CORPORATE SOURCE: Department of Gynecological Oncology, University Hospital, Uppsala, Sweden.
SOURCE: ACTA ONCOLOGICA, (1996) 35 Suppl 5 50-4. Ref: 30
Journal code: 8709065. ISSN: 0284-186X.
PUB. COUNTRY: Norway
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199705
ENTRY DATE: Entered STN: 19970602
Last Updated on STN: 19970602
Entered Medline: 19970522

AB **Bisphosphonates** exert their analgesic effect by several mechanisms. The long-term effects are probably due to osteoclast inhibition. The acute pain-relieving effect, which occurs within days or a week, is likely to be associated with the reduction of various potentially pain-producing substances. As regards pamidronate, several open, controlled studies have shown a significant effect on bone pain in 30-70% of breast cancer patients. The effects have been dose-dependent: a mean dose of 15 mg i.v./week is obviously suboptimal, whereas higher doses yield markedly better effects. The dose response is most evident at doses between 15 and 30 mg/week. Furthermore, the total dose per infusion is of interest: 30 mg every 2 weeks is an ineffective treatment, whereas 60 mg every 4 weeks is more effective. Thus, both the dose per week and the total dose per infusion are of importance in order to achieve optimal treatment. Patients with rapid progression of their disease require higher doses than patients with slow progression. **Parenteral** therapy is more effective than oral treatment. Both oral and **parenteral** clodronate exert a significant, positive effect on total skeletal morbidity and thus probably also on bone pain. Unfortunately, pain measurements have not been performed and evidence for pain reduction is indirect. Specific pain studies and studies of quality of life, with few exceptions, are, however, still lacking.

ACCESSION NUMBER: 2001493530 MEDLINE
DOCUMENT NUMBER: 21427461 PubMed ID: 11535969
TITLE: [Use of clodronic acid in mineral metabolism conditions: state of the art in 2000].
Impiego del clodronato nei disordini del metabolismo minerale: stato dell'arte nell'anno 2000.
AUTHOR: Brandi M L
CORPORATE SOURCE: Dipartimento di Medicina Interna, Universita degli Studi, Firenze, Italy.
SOURCE: MINERVA MEDICA, (2001 Aug) 92 (4) 251-68. Ref: 120
Journal code: 0400732. ISSN: 0026-4806.
PUB. COUNTRY: Italy
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: Italian
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20010906
Last Updated on STN: 20020122
Entered Medline: 20011227

AB Clodronic acid is a non-aminate **bisphosphonate** capable of inhibiting bone resorption. Pharmacological and clinical trials have shown the efficacy of clodronic acid in the treatment of post-menopausal osteoporosis and in all conditions of excess bone resorption, such as Paget's disease, malignant tumoral hypercalcemia and osteolytic metastases. Clodronic acid is the only **bisphosphonate** currently on the market available for both oral and **parenteral** administration. Intramuscular therapy with clodronic acid at a dose of 100 mg/week has shown significant effects on bone mineral density after 6 months treatment in patients with postmenopausal osteoporosis and these effects were maintained 3 years after the start of treatment. Increased bone mass is associated with a reduced risk of the onset of vertebral fractures. In a recent three-year study a significant increase was observed in bone mineral density associated with a 46% reduction in the incidence of vertebral fractures. The reduction in bone pain after **parenteral** treatment with clodronic acid is an important added value in the use of this molecule in osteopenic pathologies. Moreover the costs of **parenteral** clodronic acid treatment is certainly competitive compared to other drugs. Oral and **parenteral** clodronic acid was well tolerated in clinical trials. Gastrointestinal adverse effects were described only with high oral doses. These effects were transient and generally resolved without interrupting the treatment. Clodronic acid is an effective and well tolerated drug able to inhibit bone resorption. The low incidence of undesired effects at a gastroenteric level, the possibility of formulas for **parenteral** administration, the antalgic effect and low costs make clodronic acid an extremely interesting molecule for the prevention and treatment of postmenopausal osteoporosis and all conditions of excessive bone resorption, such as Paget's disease, malignant tumoral hypercalcemia, osteolytic metastasis and hyperparathyroidism.

L17 ANSWER 32 OF 139 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 1995:128514 BIOSIS

DOCUMENT NUMBER: PREV199598142814

TITLE: A prospective, controlled, non-randomized study on prophylactic **parenteral** dichloromethylene **bisphosphonate** (clodronate) in multiple myeloma.

AUTHOR(S): Riccardi, Alberto [Reprint author]; Ucci, Giovanni; Brugnatelli, Silvia; Mora, Oreste; Merlini, Giampaolo; Piva, Nadia; De Paoli, Alberto; Barbarano, Luciana; Di Stasi, Michele; Alberio, Franco; Nicoletti, Giovanni; Morandi, Sergio; Rinaldi, Elena; Piccinini, Lino; Ascari, Edoardo

CORPORATE SOURCE: Clinica Med. II, Policlinico S. Matteo, 27100 Pavia, Italy

SOURCE: International Journal of Oncology, (1994) Vol. 5, No. 4, pp. 833-839.
ISSN: 1019-6439.

DOCUMENT TYPE: Article

LANGUAGE: English

ENTRY DATE: Entered STN: 29 Mar 1995
Last Updated on STN: 29 Mar 1995

AB Bone resorption by osteoclasts causes neoplastic bone disease, which is a significant cause of death in multiple myeloma (MM). Counteracting bone resorption with prophylactic **bisphosphonates** has delayed bone disease, and this is expected to improve survival. Between January, 1987 and March, 1990, 341 evaluable previously untreated, consecutive patients with MM entered a prospective, multicenter study in which cytostatic therapy was randomized. The first 148 patients recruited were not planned for prophylaxis and the following 193 were scheduled to receive **parenteral**, prophylactic clodronate. Clodronate was administered at a dose of 600-1000 mg/4-6 weeks and was started at diagnosis and continued throughout survival time. Data on clodronate prophylaxis were evaluated on both an intention-to-treat and a compliance analysis basis. The rate of response and the duration of response were independent of clodronate prophylaxis. Progression of skeletal disease occurred less often in patients who received the drug than in those who were not given prophylaxis (50.5 vs 34.8%; p lt .02 by compliance analysis). Survival was longer for patients on clodronate prophylaxis than for those who were not planned for (p lt .02 by intention to-treat-analysis) or for those who did not receive clodronate prophylaxis (p lt .009 by compliance analysis). Local pain associated with i.m. administration was the only significant side effect of clodronate. **Parenteral** clodronate prophylaxis prolongs survival in MM, probably because it allows better control of bone disease and reduces deaths related to it.

L17 ANSWER 29 OF 139 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:793432 CAPLUS
DOCUMENT NUMBER: 137:304812
TITLE: A drug for use in bone grafting
INVENTOR(S): Little, David Graham
PATENT ASSIGNEE(S): The Royal Alexandra Hospital for Children, Australia
SOURCE: PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002080933	A1	20021017	WO 2002-AU412	20020328
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1383509	A1	20040128	EP 2002-712634	20020328
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.:
AU 2001-4187 A 20010403
AU 2001-9613 A 20011217
WO 2002-AU412 W 20020328

AB A drug and method for bone grafting which improves the osteoinductive and/or osteoconductive potential of a bone graft, bone graft substitute or extenders. The drug is selected from the group consisting of **bisphosphonates** which may be administered to a subject either prior to, during or after a bone grafting procedure.

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 26 OF 139 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1982:411853 CAPLUS
DOCUMENT NUMBER: 97:11853
TITLE: Alkanediphosphonate inhibitors of tumor cell metastasis
INVENTOR(S): Hedglin, W. L.; Martodam, R. R.
PATENT ASSIGNEE(S): Procter and Gamble Co., USA
SOURCE: Belg., 23 pp.
CODEN: BEXXAL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
BE 890453	A1	19820322	BE 1981-206031	19810922
JP 57154131	A2	19820922	JP 1981-160054	19811007
US 4634691	A	19870106	US 1983-459164	19830119

PRIORITY APPLN. INFO.: US 1980-194750 19801007
US 1981-297462 19810828

AB 1-hydroxyethane-1,1-**diphosphonic acid** [2809-21-4], dichloromethanediphosphonic acid [10596-23-3], Or their salts or esters reduced the incidence of tumor cell metastasis in bone in animals and humans. A gelatin capsule was prepd. contg. 350 mg dichloromethanediphosphonic acid (as a mixt. of the di-Na [22560-50-5] and tri-Na [10595-91-2] salts) and 50 mg starch. Tablet and **parenteral** formulations were also prepd.

L17 ANSWER 11 OF 139 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003476359 EMBASE

TITLE: Injectable **bisphosphonates** in the treatment of postmenopausal osteoporosis.

AUTHOR: Sartori L.; Adami S.; Filipponi P.; Crepaldi G.

CORPORATE SOURCE: Dr. L. Sartori, Clinica Medica I, Dept. of Medical/Surgical Sciences, University of Padova, Via Giustiniani 2, 35128 Padova, Italy. leonardo.sartori@unipd.it

SOURCE: Aging - Clinical and Experimental Research, (2003) 15/4 (271-283).
Refs: 87
ISSN: 1594-0667 CODEN: AGNGET

COUNTRY: Italy

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 020 Gerontology and Geriatrics
030 Pharmacology
033 Orthopedic Surgery
036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Osteoporosis is a "silent" disease and the patient has usually no clue of it until the occurrence of a fragility fracture. Prevention requires a continuous daily treatment that could be uncomfortable to the patient. Besides the recently introduced weekly oral schedules, injectable **bisphosphonates** have often been used as an off-label option to ameliorate compliance. In general, although with different efficiency, almost all injectable **bisphosphonates** can improve bone mineral density and suppress bone resorption markers. The effect of intravenous infusions of **bisphosphonates** are, to a large extent, similar to equivalent intramuscular administrations, but doses and dosing intervals represent the critical issues. Pain at the injection site and acute phase reactions are relatively common to intramuscular clodronate and intravenous infusions of nitrogen-containing **bisphosphonates**, respectively. Under certain circumstances, intermittent treatment with injectable **bisphosphonates** might represent a feasible alternative when compliance is at risk. .COPYRGT. 2003, Editrice Kurtis.

L17 ANSWER 10 OF 139 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:998273 CAPLUS
DOCUMENT NUMBER: 124:37752
TITLE: Use of **bisphosphonates** for inhibiting bone resorption following implantation of orthopedic prosthesis
INVENTOR(S): Yates, Ashley J.
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: PCT Int. Appl., 18 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9528936	A1	19951102	WO 1995-US4498	19950417
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TT, UA, US, UZ				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5646134	A	19970708	US 1994-230670	19940421
TW 406021	B	20000921	TW 1995-84103056	19950330
IL 113361	A1	19991130	IL 1995-113361	19950413
CA 2188030	AA	19951102	CA 1995-2188030	19950417
CA 2188030	C	20030729		
AU 9523748	A1	19951116	AU 1995-23748	19950417
EP 756483	A1	19970205	EP 1995-916335	19950417
EP 756483	B1	20030409		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
CN 1146152	A	19970326	CN 1995-192675	19950417
CN 1078073	B	20020123		
HU 74911	A2	19970328	HU 1996-2888	19950417
JP 09512268	T2	19971209	JP 1995-527678	19950417
NZ 284295	A	20000623	NZ 1995-284295	19950417
RU 2161032	C2	20001227	RU 1996-121563	19950417
EP 1197213	A2	20020417	EP 2001-201914	19950417
EP 1197213	A3	20020925		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI				
AT 236641	E	20030415	AT 1995-916335	19950417
PT 756483	T	20030731	PT 1995-95916335	19950417
ZA 9503185	A	19951227	ZA 1995-3185	19950420
BG 63102	B1	20010430	BG 1996-100910	19961016
FI 9604213	A	19961018	FI 1996-4213	19961018
NO 9604441	A	19961018	NO 1996-4441	19961018
US 5891863	A	19990406	US 1997-876898	19970616
US 5972913	A	19991026	US 1998-82237	19980520
AU 9935747	A1	19990819	AU 1999-35747	19990618

PRIORITY APPLN. INFO.:			
US 1994-230670	A	19940421	
AU 1995-23748	A3	19950417	
EP 1995-916335	A3	19950417	
WO 1995-US4498	W	19950417	
US 1997-876898	A1	19970616	

AB Disclosed is a therapy for treating and for preventing periprosthetic bone loss by the administration of a **bisphosphonate** bone resorption inhibitor, e.g., alendronate, in patients who have an orthopedic implant device. A tablet contg. 200 mg alendronate was formulated and its effects on bone formation and resorbability of bone formed during alendronate treatment were demonstrated with a modified bone marrow ablation rat model.

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ACCESSION NUMBER: 2003476359 EMBASE

TITLE: Injectable **bisphosphonates** in the treatment of postmenopausal osteoporosis.

AUTHOR: Sartori L.; Adami S.; Filipponi P.; Crepaldi G.

CORPORATE SOURCE: Dr. L. Sartori, Clinica Medica I, Dept. of Medical/Surgical Sciences, University of Padova, Via Giustiniani 2, 35128 Padova, Italy. leonardo.sartori@unipd.it

SOURCE: Aging - Clinical and Experimental Research, (2003) 15/4 (271-283).
Refs: 87
ISSN: 1594-0667 CODEN: AGNGET

COUNTRY: Italy

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 020 Gerontology and Geriatrics
030 Pharmacology
033 Orthopedic Surgery
036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Osteoporosis is a "silent" disease and the patient has usually no clue of it until the occurrence of a fragility fracture. Prevention requires a continuous daily treatment that could be uncomfortable to the patient. Besides the recently introduced weekly oral schedules, injectable **bisphosphonates** have often been used as an off-label option to ameliorate compliance. In general, although with different efficiency, almost all injectable **bisphosphonates** can improve bone mineral density and suppress bone resorption markers. The effect of intravenous infusions of **bisphosphonates** are, to a large extent, similar to equivalent intramuscular administrations, but doses and dosing intervals represent the critical issues. Pain at the injection site and acute phase reactions are relatively common to intramuscular clodronate and intravenous infusions of nitrogen-containing **bisphosphonates**, respectively. Under certain circumstances, intermittent treatment with injectable **bisphosphonates** might represent a feasible alternative when compliance is at risk. .COPYRGT. 2003, Editrice Kurtis.

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ACCESSION NUMBER: 93080535 EMBASE
DOCUMENT NUMBER: 1993080535
TITLE: Pharmacology and clinical use of **bisphosphonates** in oncology.
AUTHOR: Musel B.; Scigalla P.
CORPORATE SOURCE: Internat. Projektentwicklung Therap., Boehringer Mannheim GmbH, Sandhofer Strasse 116,D-W-6800 Mannheim 31, Germany
SOURCE: Onkologie, (1992) 15/6 (444-453).
ISSN: 0378-584X CODEN: ONKOD2
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
033 Orthopedic Surgery
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English; German

AB The **bisphosphonates** are substances which are chemically characterized by a P-C-P bond. As analogues of pyrophosphate these compounds have a high affinity for bone mineral and only little or no effect on other tissues. Acute and chronic toxicity studies revealed the kidney as the primary target organ for toxicity. Gastrointestinal toxicity has been reported at high oral doses. No significant hematological changes and changes to the immune system have been described. The osteoprotective effect of **bisphosphonates** has been shown in various animal models with different types of tumor cells. The precise mechanism of action of the **bisphosphonates** is not clear. They have no direct effect on tumor cells but make bone more resistant against osteolysis and tumor invasion. The intestinal absorption of all **bisphosphonates** is low and highly variable. The absorbed drug is cleared rapidly from the blood and either excreted in the urine (80%) or incorporated into bone (20%). The retention half-life in bone is long and depends upon the turnover of the skeleton. **Bisphosphonates** can be used successfully in the treatment of hypercalcemia of malignancy. There are many published reports showing that the usual dose regimen of clodronate, i.v. infusion of 300 mg daily for 5 days, is effective in normalizing hypercalcemia in about 90% of patients. In a recent study, a single intravenous infusion of 1,500 mg was as effective in reducing serum calcium as the same dose give over 5 days without inducing adverse effects. In two pilot studies in multiple myeloma patients the progression of skeletal destruction and the incidence of new osteolytic lesions was reduced by long-term clodronate treatment. This finding was recently confirmed in a placebo-controlled trial in 350 newly diagnosed patients with multiple myeloma. Oral clodronate therapy for 24 months reduced the progression of osteolytic bone lesions. A significant decrease in the incidence of new osteolytic lesions was also found in a prospective study with a median follow-up of 24 months using intermittent **parenteral** clodronate. This was associated in both studies with a reduction in bone pain, hypercalcemic episodes and pathological fractures. A most interesting finding is the preliminary result of an impressive gain in bone mass within 6 months of clodronate treatment in myeloma patients in contrast to a rapid loss of bone mineral at the same time in the control group. Two further controlled studies are now in progress examining the long-term effects of clodronate in multiple myeloma. A double-blind, placebo-controlled study in 173 patients with bone metastases due to breast cancer demonstrated that antiosteolytic therapy decreased the morbidity from skeletal complications. Treatment with oral clodronate (1,600 mg/day) significantly reduced the number of hypercalcemic episodes and the incidence of vertebral fractures compared to placebo. Improvement in bone pain was demonstrated by reduced radiotherapy requirements for spinal bone pain in the clodronate group. A similar effect had been noted

previously in an open study with pamidronate in patients with bone metastases due to advanced breast cancer. An increase in bone mineral density of the lumbar spine was also found in breast cancer patients after clodronate treatment. In patients with bone metastases due to prostate cancer a symptomatic benefit of **bisphosphonate** therapy has been observed in studies with continuous oral treatment or with intermittent intravenous administration of clodronate. A dosage regimen of 300 mg clodronate daily as intravenous infusion for 1 week followed by oral maintenance of 1,600 mg/day induced definite pain relief in patients with progressive hormone-refractory prostate cancer. Symptomatic improvement was also found with oral administration of clodronate in a placebo-controlled trial including 81 patients with prostatic cancer. The beneficial effect of antiosteolytic agents, particularly clodronate, in tumor-induced hypercalcemia and osteolysis appears to be well-established and holds the promise to improve the quality of life of cancer patients by decreasing the incidence of bone pain, hypercalcemia and fractures.